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Review

Post-thrombotic syndrome – Recent aspects of prevention, diagnosis and clinical management

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ABSTRACT

Post-thrombotic syndrome (PTS) is the most frequent chronic complication of acute deep vein thrombosis (DVT). However, gaps in our current understanding of the risk factors, diagnostic criteria, preventive strategies, and even treatment modalities for PTS prevent clinicians from employing measures that could reduce the occurrence of this disorder and the associated morbidity. This review provides an overview of the important elements of PTS, including recent multifaceted aspects related to its definition, pathophysiology, risk factors, prevention and management.

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1. Introduction

Post-thrombotic syndrome (PTS) is the most frequent chronic complication of acute deep vein thrombosis (DVT), occurring in 20–40% of patients with DVT and severe symptoms developing in 5–10% of such patients [1–3]. PTS has a significant negative impact on quality of life (QOL) outcomes and health care costs [4]. PTS can be diagnosed clinically after a previous objective diagnosis of DVT in the absence of specific laboratory imaging or functional tests [3]. The signs and symptoms of PTS vary from patient to patient and may include edema, heaviness, leg pain, eczema, hyperpigmentation, lipodermatosclerosis, and venous ulcers. However, PTS and primary valvular insufficiency share signs and symptoms of chronic venous insufficiency, making correct diagnosis of PTS difficult. The present review focuses on the features of PTS, reviewing its definition, pathophysiology, risk factors, diagnosis, prevention and management.

2. Definition of PTS

Despite increasing awareness of PTS as a common and important complication of DVT, there is no gold standard objective test to establish its presence, and PTS is diagnosed primarily on the basis of typical symptoms and clinical signs in limbs affected by DVT. Several scoring systems or classifications for grading the severity of PTS have been proposed [3], including the Villalta scale [5], Ginsberg measure [6] and Brandjes score [7]. On the other hand, the Widmer [8] and Clinical, Etiologic, Anatomic, and Pathophysiologic (CEAP) [9] classifications, and the Venous Clinical Severity Score (VCSS) [10] were originally developed for patients with chronic venous insufficiency (CVI), but can be applied to cases of PTS.

2.1. Villalta scale

The Villalta scale was designed specifically for patients with PTS and introduced in an abstract in 1994 as a disease-specific assessment questionnaire for diagnosis and classification of the severity of PTS. The Villalta scale (Table 1) assesses five symptoms (pain, cramps, heaviness, paresthesia, pruritus) and six clinical signs (pretibial edema, skin induration, hyperpigmentation, redness, venous ectasia, pain on calf compression). Each variable has a 4-point scale ranging from 0 (absent) to 3 (severe). PTS is diagnosed if the Villalta score is ≥ 5 or if a venous ulcer is present. A score of 5–9 is categorized as mild, 10–14 as moderate, and ≥ 15 as severe disease. The subcommittee for Control of Anticoagulation of the International Society for Thrombosis and Hemostasis has recommended the Villalta scale as the most appropriate method for diagnosis of PTS [11]. Furthermore, a recent systematic review of various scoring systems for PTS revealed that the Villalta score, combined with a venous disease-specific quality of life questionnaire, was the most suitable gold standard for diagnosis and classification of PTS [12].

Table 1
Villata scale [5].

Symptoms/clinical signs	*None*	*Mild*	*Moderate*	*Severe*
Symptoms	0 points	1 point	2 points	3 points
Pain	0 points	1 point	2 points	3 points
Cramps	0 points	1 point	2 points	3 points
Heaviness	0 points	1 point	2 points	3 points
Paresthesia	0 points	1 point	2 points	3 points
Pruritus	0 points	1 point	2 points	3 points
Clinical signs	0 points	1 point	2 points	3 points
Pretibial edema	0 points	1 point	2 points	3 points
Skin induration	0 points	1 point	2 points	3 points
Hyperpigmentation	0 points	1 point	2 points	3 points
Redness	0 points	1 point	2 points	3 points
Venous ectasia	0 points	1 point	2 points	3 points
Pain on calf compression	0 points	1 point	2 points	3 points
Venous ulcer	Absent			Present

2.2. Ginsberg measure

The Ginsberg measure was designed on the basis of persistence of symptoms or development of new symptoms 6 months after an initial DVT. The recommended criteria for the Ginsberg measure are as follows:

- Persistent swelling and leg pain for 1 month after DVT
- Pain and swelling developing 6 months after DVT
- Relieved by rest and elevation

Kahn et al. carried out a clinical study comparing the Villalta scale and the Ginsberg measure, and found that the proportion of patients classified as having PTS was almost 5-fold higher with the Villalta scale than with the Ginsberg measure, and that the agreement between the two measures was poor at 1 year after DVT [13]. They concluded that the Ginsberg measure identifies more severe disease.

2.3. Brandjes score

The Brandjes score was developed to assess the effect of compression stockings on patients with symptomatic proximal DVT. The Brandjes score is composed of objective symptoms and subjective signs, and these variables are graded as absent or present (Table 2). A diagnosis of mild-moderate PTS is made if the score is 3 or higher (including one objective criterion), whereas a diagnosis of severe PTS is established if the score is 4 or more.

Table 2
Brandjes score [7].

Subjective criteria Symptoms	Score	Objective criteria Signs	Score
Spontaneous pain in calf	1	Calf circumference increased by 1 cm	1
Spontaneous pain in thigh	1	Ankle circumference increased by 1 cm	1
Calf pain on standing/walking	1	Pigmentation	1
Thigh pain on standing/walking	1	Venectasia	1
Edema of foot/calf	1	Newly formed varicosis	1
Heaviness of foot/calf	1	Phlebitis	1
Spontaneous pain and pain on walking/standing	1	Venous ulcer	4
Impairment of daily activities	1		

Table 3
Widmer classification [8].

Stage	*Symptoms*
1	Ankle flare
	Subclinical edema
2	Edema
	Pigmentation
	Lipodermatosclerosis
	White (skin) atrophy
3	Leg ulcer
	Leg ulcer in the past

2.4. Widmer classification

The Widmer classification was originally developed for grading the severity of CVI, but has also been utilized for PTS. This classification grades patients into classes I, II and III (Table 3) based mainly on clinical signs, and is still widely used in German-speaking countries.

2.5. CEAP classification

The CEAP classification was developed to categorize chronic venous disease (CVD) according to clinical signs (C), etiology (E), anatomic distribution (A), and pathophysiology. This classification subdivides patients into eight classes according to the clinical severity (Table 4). Use of the CEAP classification is especially widespread among physicians specializing in vascular conditions, and can also be used for assessment of PTS. However, these tools lack a consensus "cut-off" for classification of the PTS category. For example, while Yamaki et al., using the CEAP classification, defined a clinical signs score of ≥ 4 as diagnostic for PTS [14], others have used a score of ≥ 3 for the PTS category [15,16]. In a prospective study of 40 limbs in 34 patients with established PTS, Lattimer et al. found a good correlation between the Villalta scale, VCSS and CEAP classifications [17].

2.6. VCSS

The VCSS was developed from elements of the CEAP classification, but was not designed to replace the latter. The VCSS is evaluative and longitudinal, while the CEAP classification is descriptive and relatively static (Table 5). Thus, it is designed to give additional weight to more severe manifestations of CVD (CEAP clinical class 4–6). The VCSS has been used and evaluated in multiple studies with varied results [18,19]. However, there is no standard VCS score for diagnosing or grading the severity of PTS. Furthermore, Meissner et al. found that the component scores for pain, inflammation, and pigmentation showed significant inter-observer variability, even if the VCSS showed a good correlation with the CEAP classification [20]. Accordingly, the VCSS is not used to diagnose the presence of PTS but rather for measurement of disease severity.

Table 4
CEAP clinical classification [9].

Class	*Signs*
C_0	No visible or palpable signs of venous disease
C_1	Telangiectasias or reticular veins
C_2	Varicose veins; distinguished from reticular veins by a diameter of 3 mm or more
C_3	Edema
C_{4a}	Pigmentation or eczema
C_{4b}	Lipodermatosclerosis or atrophic blanche
C_5	Healed venous ulcer
C_6	Active venous ulcer

3. Pathophysiology of PTS

The pathophysiologic mechanism whereby PTS develops after DVT is not fully understood. Clinical observations have shown that a blood clot forming in the deep veins of the lower extremity can cause inflammation and interrupt venous blood flow to the heart, causing severe damage to the vein valves, making them leaky and allowing retrograde blood flow to the ankle. Such venous blood flow interruption and retrograde blood flow can cause venous hypertension, thereby leading to hyperpigmentation, corona phlebectatica, lipodermatosclerosis or ulceration. These processes include leukocyte activation, adhesion and migration through the basement membrane with release of growth factors and proteases [21].

Experimental observations have revealed that leukocytes mediate the release and activation of metalloproteinase 2 (MMP-2) and MMP-9, as well as promoting vein wall fibrosis. Vein wall remodeling after DVT is similar to wound healing, and is associated with increased expression of the procollagen gene and total collagen [22]. This is associated with increased early expression of MMP-9, followed by MMP-2 expression and activity after DVT resolution. Another study has shown that post-thrombotic vein wall remodeling is impaired in cystine-cystine receptor 7 (CCR7) $(-/-)$ mice, which have a profibrotic phenotype, is dependent on a thrombotic mechanism, and is mediated by circulating CCR7$(+)$ cells [23]. CCR7$(+)$ signaling may play an important role in positive vein wall remodeling after a thromboembolic event.

4. Factors associated with the risk of developing PTS

The factors associated with the risk of developing PTS are not well understood. For this reason, it is difficult to reliably identify which patients are likely to develop PTS in the acute phase of DVT.

4.1. Patient characteristics at initial onset of DVT

Among 1916 patients participating in the Multiple Environmental and Genetic Assessment (MEGA) study of risk factors for DVT, the 1-year cumulative incidence of PTS was 25% with a cumulative incidence of 7% for severe PTS [24]. Compared to male patients, women were at higher risk of PTS [risk ratio (RR) 1.5, 95% confidence interval (CI) 1.3–1.8] [24]. Similarly, obese patients had a 1.5-fold (RR 1.5, 95% CI 1.2–1.9) increased risk of PTS compared with individuals with a normal body mass index (BMI) [24]. However, the role of higher BMI in the development of PTS is still being debated [12]. Patients with varicose veins also had an increased risk of PTS (RR 1.5, 95% CI 1.2–1.8). Concerning the initial anatomic distribution of DVT, patients who had thrombus in the ilio-femoral venous segment had 1.3-fold risk of PTS compared with those who had femoro-popliteal DVT (RR 1.3, 95% CI 1.1–1.6) [24], whereas another study revealed a high risk of developing PTS in patients who had distal DVT [25]. In contrast, older patients were less likely to develop PTS (RR 0.6, 95% CI 0.4–0.9) [24]. Moreover, the presence of factor V Leiden or prothrombin gene mutation is reportedly an independent predictor of a lower risk of PTS [26].

4.2. Recurrent DVT

Several studies have identified ipsilateral recurrent DVT as a strong risk factor for PTS [27–30]. Ipsilateral recurrent DVT was found to be associated with a 6–10-fold risk of PTS. Several factors

Table 5
VCSS [10].

Descriptor	None: 0	Mild: 1	Moderate: 2	Severe: 3
Pain	None or focal	Occasional pain or other discomfort	Daily pain or other discomfort	Daily pain or discomfort
Varicose veins (> 4 mm diameter)		Few, scattered: branch varicosities	Confined to calf or thigh	Involves calf and thigh
Venous edema		Limited to foot and ankle area	Extends above ankle but below knee	Extends to knee and above
Skin pigmentation		Limited to perimalleolar area	Diffuse over lower third of calf	Wider distribution above lower third of calf
Inflammation		Limited to perimalleolar area	Diffuse over lower third of calf	Wider distribution above lower third of calf
Induration		Limited to perimalleolar area	Diffuse over lower third of calf	Wider distribution above lower third of calf
Active ulcer number	0	1	2	≥ 3
Active ulcer duration	N/A	< 3 months	> 3 months but < 1 year	Not healed for > 1 year
Active ulcer size	N/A	Diameter < 2 cm	Diameter 2–6 cm	Diameter > 6 cm
Use of compression therapy	0 Not used	1 Intermittent use of stockings	2 Wears stockings most days	3 Full compliance: stockings

affect the development of recurrent thromboembolic events during the course of treatment. Hull et al. found that subtherapeutic anticoagulation early in the course of treatment (first 24 h) increased the risk of recurrent VTE events 15-fold [31]. Compared to unfractionated heparin, greater thrombus resolution followed by reduction in post-thrombotic morbidity was found with the use of low-molecular-weight heparin (LMWH) in the early stage of DVT treatment [32]. Moreover, Young et al. reported that recurrent DVT risk was increased [hazard ratio (HR) 2.2] in patients in whom residual thrombus was found on follow-up duplex ultrasound [33]. Recently, a direct thrombin inhibitor (Dabigatran) and factor Xa inhibitor (Apixaban) have been proven to facilitate quicker clot lysis and recanalization than warfarin in an experimental model. Future studies investigating these effects of direct oral anticoagulants (DOAC) on clot lysis in humans are warranted [34–36].

4.3. Duration and intensity of oral anticoagulation

The duration of anticoagulation also affects the incidence of recurrent DVT. Recurrent VTE is expected to develop in at least 30% of patients after receiving oral anticoagulant therapy for 3–6 months [37,38]. Schulman et al. carried out a multicenter trial comparing six weeks of oral anticoagulation with six months of the same treatment in patients with a first episode of DVT, and found that the latter resulted in lower recurrence of DVT than the former [37]. Patients with permanent risk factors for VTE (e.g. active cancer, immobilization, antiphospholipid syndrome) and those with unprovoked VTE had a higher incidence of VTE than those with transient risk factors including hormone replacement therapy, minor injury, pregnancy and long-distance travel [38]. Kahn et al. found no significant difference in the risk of developing PTS between patients who had warfarin therapy with an international normalized ratio (INR) of 1.5–1.9 and those with an INR of 2.0–3.0 [39]. In contrast, Chitsike et al. reported that patients who had subtherapeutic anticoagulation (INR < 2) had a higher risk of developing PTS than those who had therapeutic oral anticoagulant therapy [odds ratio (OR) 1.88 95% CI 1.15–3.07] [40].

4.4. Venous abnormalities detected by duplex ultrasound

Residual venous thrombus and development of venous reflux increase the risk of PTS development over time. In a study involving 120 lower extremities of 105 patients who had a first episode of DVT, Labropoulos et al. reported that limbs with both reflux and obstruction were more likely to develop skin damage than those with reflux or obstruction alone [41]. Comerota et al. investigated the relationship between residual thrombus and symptoms of PTS and found a direct and significant correlation of CEAP clinical class ($r^2=0.74$) and Villalta score ($r^2=0.61$) with residual thrombus, suggesting that residual thrombus is associated with an increased risk of PTS [42]. In contrast, Yamaki et al. reported that the presence of reflux, as reflected by elevated peak reflux velocity in the axial deep veins, mainly in the popliteal (> 25.4 cm/s, OR 60.32) and (> 24.5 cm/s, OR 25.77) femoral veins was a strong independent predictor of advanced PTS [43]. However, they did not find any significant correlation between progression of PTS symptoms and reflux time, which is now considered the gold standard for diagnosis of venous reflux. Latella et al. also found that valvular reflux in the popliteal vein was independently associated with moderate to severe PTS (OR 2.72 compared with no or mild PTS, 95% CI 1.25, 5.90) [44].

4.5. Abnormal biomarkers

Several investigators have tested the possible correlation between elevated D-dimer levels and development of PTS. Latella et al. found that the mean D-dimer level at 4 months after DVT was significantly higher in patients who developed PTS than in those who did not [44]. In contrast, Galanaud et al. evaluated D-dimer levels after discontinuation of anticoagulants but found no significant association with the development of PTS [45]. The association between fibrinogen level and PTS development has also been studied by several investigators, but no correlation was evident [46,47].

With regard to other markers predictive of PTS, Rabinovich et al. conducted a systematic review of the association between inflammatory biomarkers and PTS. However, the results were conflicting, and only intercellular adhesion molecule (ICAM)-1 was suggested to be a promising marker for further investigation [48].

4.6. Hemodynamic changes in patients with PTS

Using air plethysmography (APG), Lattimer et al. compared the Villalta scale with the VCSS, CEAP classification and venous hemodynamics using the venous filling index (VFI) [17]. They found a meaningful correlation of VFI with the Villalta ($r=0.499$) scale and VCSS ($r=0.480$) and concluded that VFI may provide a clinically meaningful venous hemodynamic parameter for evaluation of PTS. In the presence of proximal venous occlusion, however, VFI obtained by APG may underestimate the magnitude of venous reflux [49].

Several investigators have applied various plethysmographic methods for detection of arterial perfusion, and found increased resting arterial perfusion and reduced arterial inflow during the hyperemic response in patients with severe chronic venous disorders [50–53]. These findings lend support to the view that

chronic venous insufficiency is a condition that affects both the venous and arterial systems of the lower extremities at the microcirculation level. The disadvantages of plethysmographic examination include the use of different measuring systems for assessment of venous and arterial inflows. Accordingly, little is known about the venous and arterial interrelationship in patients with chronic venous diseases revealed using various forms of plethysmography.

Changes in calf muscle deoxygenated hemoglobin (HHb) levels have been investigated by several authors using near-infrared spectroscopy (NIRS). Hosoi et al. first applied this modality for assessment of hemodynamics in patients with CVI. They used the ambulatory venous retention index (AVRI) obtained from serial HHb changes as a parameter, and found that NIRS was useful for evaluation of ambulatory venous dysfunction [54]. They then studied symptomatic PTS, and found that the AVRI was correlated well with clinical severity [55]. Yamaki et al. also found that a higher retention index predicted the development of severe PTS symptoms [56,57].

Later, Yamaki et al. developed a new method for identifying changes in calf muscle oxygenated hemoglobin (O_2Hb) and HHb using NIRS in patients with CVD [58]. Using this protocol, they found significant differences in O_2Hb and HHb changes between patients with and those without established PTS as follows:

- On standing, the time taken until the maximum increase in O_2Hb ($_TO_2Hb_{st}$) and the oxygenation index (HbD_{st}) were significantly decreased in patients with PTS in comparison to those without.
- During exercise, venous expulsion ($\Delta HHbE_{ex}$) was significantly decreased and $\Delta HHbR_{ex}$ was significantly increased in patients with PTS.
- Decreases in the oxygenation index during exercise (HbD_{ex}) were more pronounced in patients with PTS [59]

They also found that $_TO_2Hb_{st} \leq 48$ s was the only NIRS-derived predictor of PTS at the 6-month follow-up point (OR 53.73, 95% CI: 8.43–342.41). They concluded that NIRS-derived O_2Hb appeared to reveal the earliest change in PTS, rather than the change in HHb, during follow-up of patients with DVT [60].

5. Prevention of PTS

To prevent the development of PTS, three main methods have been applied to date: thromboprophylaxis, elastic compression stockings (ECSs) and thrombolysis.

5.1. Thromboprophylaxis

A current existing guideline for antithrombotic therapy recommends anticoagulation for 3 months over (i) treatment for a shorter period (Grade 1B), (ii) treatment for a longer time-limited period (e.g., 6, 12, or 24 months) (Grade 1B), or (iii) extended therapy (no scheduled stop date) (Grade 1B) [61]. However, the risk of recurrent DVT increases over time after withdrawal of oral anticoagulants. In a randomized study that included 897 patients who were assessed at the 10-year follow-up point, Schulman et al. found no additional benefit of warfarin for 6 months over a shorter 6-week administration period [62]. In comparison with warfarin, González-Fajardo et al. found that LWMH was associated with a higher frequency of thrombus regression and a lower prevalence of recurrent VTE and PTS [63].

5.2. Elastic compression stockings

The application of ECSs after DVT is widely accepted to prevent the development of PTS. Compression therapy is believed to reduce leg edema, promote venous blood return and improve venous pump function, and compression therapy has been the first choice for prevention of PTS [64]. Several randomized clinical trials (RCTs) have supported the use of ECSs for PTS prevention. Brandjes et al. stratified patients into ECS and no-stocking groups for assessment of outcome after DVT, and reported a 50% reduction in the incidence of PTS [7]. Previous systematic reviews of the effectiveness of ECS reported a 48–54% relative risk reduction [65–67]. In contrast, Kahn et al. conducted multicenter randomized placebo-controlled trial of active versus placebo ECSs applied for 2 years for prevention of PTS [68]. The primary outcome of the study was PTS diagnosed at 6 months or later using Ginsberg's criteria (leg pain and swelling for ≥ 1 month). The cumulative incidence of PTS was 14.2% for active ECS versus 12.7% for placebo ECS (HR 1.13, 95% CI 0.73–1.76; $p=0.58$), and concluded that ECS did not prevent PTS after a first episode of proximal DVT.

In a recent systematic review addressing the effectiveness of ECS including 5 RCTs, Bernstein reported that the HR for PTS with ECSs was 0.69 (95% CI 0.47–1.02). All 5 studies also suggested no effect of ECSs on VTE recurrence (RR 0.88; 95% CI, 0.63–1.24) [69]. Accordingly, a recent guideline for antithrombotic therapy does not recommend routine use of ECSs to prevent PTS in patients with acute DVT (Grade 2B) [61].

5.3. Thrombolysis

Active thrombus removal may improve venous blood circulation, preserve valvular function, and thus reduce the risk of PTS. Because patients with extensive DVT, particularly these with ilio-femoral DVT, have a higher risk of developing PTS than those with without, early clot lysis may lead to reduction of post-thrombotic sequelae [70,71]. Previous studies addressing the efficacy of systemic thrombolysis found a significant improvement in clot lysis. A review by Watson and Armon reported a significant improvement in complete clot lysis (RR 4.14, 95% CI 1.22–14.01), which was maintained at longer-term follow-up (RR 2.71, 95% CI 1.84–3.99) [72]. Other trials have demonstrated a lower prevalence of PTS development in patients who received plasminogen activator compared with these who received heparin [73,74].

To obtain successful clot lysis, a plasminogen activator needs to act on a large clot surface [75]. For this reason, currently, endovascular therapies have replaced previously attempted systemic thrombolytic therapies because of their higher efficiency, and several RCTs have been published. An improved QOL was also reported in patients receiving catheter-directed thrombolysis (CDT) compared with these receiving anticoagulation alone [76].

Elsharawy et al. carried out a randomized study comparing CDT with standard anticoagulation in patients with ilio-femoral DVT, and found a significantly higher proportion of complete clot lysis in patients who received CDT than in those who received anticoagulation (72% vs. 12%, $p < 0.001$) [77]. The TORPEDO trial revealed a significant reduction of VTE recurrence (2.3% vs. 14.8%, $p=0.003$) and PTS incidence (3.4% vs. 27.2%, $P=0.001$) at the 6-month follow-up point in patients treated with CDT. The CaVenT study evaluated 24-month outcome data in patients with ilio-femoral DVT who were randomly assigned to conventional treatment alone or conventional treatment with additional CDT [78]. After 24 months of follow-up, the incidence of PTS was significantly decreased in patients allocated additional CDT relative to those who received conventional treatment (41.1% vs. 55.6%, $p=0.047$). This corresponded to an absolute risk reduction of $14 \cdot 4\%$ (95% CI 0.2–27.9), and the number who required treatment

was 7 (95% CI 4–502). It was also found that major bleeding complications were more frequent in the treatment group than in the control group ($p=0.003$). Notably, the CaVenT study evaluated outcome during an extended duration of follow-up [79]. At the 5-year follow-up point, 37 patients (43%; 95% CI 33–53) allocated to catheter-directed thrombolysis developed PTS, compared with 63 (71%; 95% CI 61–79) allocated to the control group ($p < 0.0001$), corresponding to an absolute risk reduction of 28% (95% CI 14–42) and a number who required treatment of 4 (95% CI 2–7). Despite these favorable results with the use of CDT for prevention of PTS, this therapy failed to improve QOL [79]. The ATTRACT study is a health-sponsored, Phase III, multicenter RCT designed to compare pharmacomechanical catheter-directed thrombolysis (PCDT)+ standard therapy with standard therapy alone for treatment of proximal DVT. This study started in 2013 and is still ongoing [80]. The primary study hypothesis is that PCDT will reduce the incidence of PTS within 2 years by one-third, as assessed using the Villalta Scale.

Percutaneous mechanical thrombectomy (PMT) devices are also a minimally invasive adjunctive treatment option for decreasing the incidence of PTS. A single-center prospective study by Engelberger found that ultrasound-assisted CDT yielded a high rate of venous patency with a low risk of bleeding complications in patients with ilio-femoral DVT [81]. Karthikesalingam et al. reviewed 16 prospective case series including 481 patients who received rheolytic, rotational, or ultrasound-assisted PMT [82]. These various devices all appeared to be safe with no procedure-related deaths or stroke; the incidence of PE was $<1\%$ and bleeding complications occurred in 6 studies out of 16. This review reported little substantial evidence to support routine use of PMT over CDT alone. Despite the increasing evidence for use of endovascular techniques for acute DVT, the 10th Edition of the Antithrombotic Guideline did not change the level of recommendation (Grade 2C) [61].

5.4. Surgical thrombectomy

Surgical thrombectomy provides an improved patency rate and a decreased incidence of PTS. Plate et al. evaluated the 10-year outcome of patients with ilio-femoral DVT who were randomly assigned to receive either conventional anticoagulation or thrombectomy combined with a temporary arteriovenous fistula and anticoagulation. They found that iliac vein occlusion was more common in the medically treated group than in the surgically treated group (59% vs. 17%, $p < 0.05$) [83].

6. Management of PTS

Currently, treatment options for PTS are limited, and no uniform protocols have been established.

6.1. Use of a compression device

ECSs have been considered a first-line treatment option for PTS. However, the benefit of ECSs for amelioration of PTS symptoms has been widely debated. Patients who have PTS are usually given stockings with a higher strength (30–40 mmHg). Ginsberg et al. randomly stratified 35 patients with symptomatic PTS into an active 30–40 mmHg compression stockings group and a placebo stockings group and found no significant inter-group difference in the proportion of treatment failure (61.1% vs. 58.8%, $p > 0.99$) [84]. On the other hand, Volikova et al. used high-frequency ultrasound to investigate the effect of compression on dermal thickness in patients with PTS [85]. They found that patients with venous ulcers had a significantly greater dermal thickness than patients without ulcers ($p=0.002$). However, dermal thickness returned to the normal control level after compression therapy. They also found a cutoff of 1.985 mm for prediction of severe PTS with a positive predictive value of 46.9% and a negative predictive value of 90.3%.

Intermittent pneumatic compression (IPC) can counteract the elevated venous pressure in patients with established PTS. For PTS patients in whom ECSs are ineffective, an IPC device can be an alternative for moderate or severe cases. Among patients with venous leg ulcers, the use of IPC for 4 h daily combined with standard wound care and compression was reported to significantly promote wound healing ($p=0.009$) [86]. Another small clinical study involving 15 patients with PTS revealed that IPC to 40 mmHg relieved severe edema in some cases [87]. In a study of the mechanisms of fibrinolytic enhancement with IPC, Comerota et al. found a striking increase of fibrinolytic activity at 180 min in both normal subjects and PTS patients ($p=0.01$–0.001) [88]. However, both baseline and stimulated fibrinolytic activity were decreased in PTS patients.

The Venowave was developed to assist venous return for treatment of severe PTS. O'Donnell et al. carried out a two-center, placebo-controlled double-blind crossover RCT involving 32 patients who were divided into a Venowave arm and a control device arm [89]. Two eight-week periods of treatment were separated by a four-week washout period, and clinical success was achieved in 31% of patients in the Venowave arm compared with 13% in the control device arm ($p=0.11$). Similarly, neuromuscular electrostimulation is known to enhance lower limb blood perfusion. Jawad et al. compared changes in blood flow by applying either a neuromuscular electrostimulation device (geko™) or IPC devices, and found that the former was superior to the latter in increasing both venous and arterial blood volume by 30% ($p < 0.001$) [90]. Griffin et al. measured changes blood flow in axial deep veins with and without the geko™ [91]. Increases in peak velocity were found in the peroneal vein (216%), the posterior tibial vein (112%) and the gastrocnemius vein (137%) in the geko™ group. Similarly, the ejected volume per stimulus was increased by 113% in the peroneal vein, 38% in the posterior tibial vein and 50% in the gastrocnemius vein. Consequently, The National Institute for Health and Care Excellence (NICE) in England has endorsed use of the geko™ device for individuals with a high risk of VTE when standard methods of prophylaxis are unsuitable or cannot be used [92]. However, further studies will be required to clarify whether such hemodynamic enhancement with a neuromuscular electrostimulator could also be beneficial for patients with PTS [93].

6.2. Pharmacologic therapy

The effect of pharmacologic therapy for patients with PTS is unclear. A review by Cochrane evaluated the effect of pentoxifylline for venous leg ulcers in 12 studies involving a total of 864 patients. The conclusion of the review was that pentoxifylline is more effective than placebo for ulcer healing (RR 1.70 95% CI 1.14–2.24), that pentoxifylline combined with compression is more effective than placebo combined with compression (RR 1.56 95% CI 1.14–2.13), and that pentoxifylline with no compression is more effective than placebo or no treatment (RR 2.25 95% CI 1.49–3.39). In contrast, the Cochran Vascular Group reviewed three studies with a total of 233 participants who were treated with rutosides (platelet aggregation inhibitors) [94]. Compared with ECSs or placebo, there were no significant differences in the improvement or deterioration of PTS symptoms in patients treated with rutosides; the odds of an improvement in PTS in patients treated with rutosides relative to patients treated with ECSs was 29%. However, the review found no evidence that rutosides were superior to the use of placebo or ECSs. A meta-analysis of five studies evaluating

micronized purified flavonoid fraction (MPFF) for ulcer healing found that complete ulcer healing occurred in 61% of patients in the MPFF group and 48% of control patients (RR 32% 95% CI 3–70%). Finally, a Cochrane review evaluated the use of horse chestnut seed extract for treatment of chronic venous insufficiency, and concluded that it did relieve symptoms including leg pain and edema in the short term [95].

6.3. Exercise

In a two-center RCT conducted by Kahn et al., patients with mild to moderate PTS were randomized to receive a six-month exercise training program or control treatment [96]. Exercise training was associated with improvement in the Venous Insufficiency Epidemiological and Economic Study Quality of Life (VEINES-QOL) scores (6.0 ± 5.1 for the exercise group versus 1.4 ± 7.2 for the control group, 95% CI 0.54–8.7; $p=0.027$) and improvement in the Villalta scale scores (-3.6 ± 3.7 versus the control group; mean change -1.6 ± 4.3, 95% CI -4.6 to 0.6; $p=0.14$). It was concluded that exercise training might improve PTS. A large RCT will be necessary to confirm whether exercise training could be potentially useful for amelioration of PTS symptoms.

6.4. Stent placement for chronic obstructive venous segment

Several investigators have reported the efficacy of venous stenting for chronic obstructive venous segment in terms of clinical symptoms, venous outflow and calf muscle pump function [97–99]. Raju reviewed peer-reviewed reports of iliac vein stenting that involved >1500 patients [100]. All of the reports were for single-arm retrospective series. In these studies, iliac vein stenting achieved a 90–100% patency rate for non-thrombotic iliac vein lesions (NIVL) and 74–89% for PTS, with a venous ulcer healing rate of 58–90%. Wen-da et al. conducted a systematic review of 14 studies of stent placement therapy for obstructive CVD [101], and found that the rate of ulcer healing was 70.3% (95% CI 59.0–79.5%) for PTS and 86.8% (95% CI 69.6–95.1%) for NIVL. The ulcer recurrence rate was 8.7% (95% CI 5.3–14.0%), and the primary, assisted primary, and secondary patency rates were 91.4%, 95.0%, and 97.8%, respectively, at 12 months and 77.1%, 92.3%, and 94.3%, respectively, at 36 months. Although, the patency rates for PTS were lower, stents may be relatively effective in patients with PTS.

6.5. Percutaneous prosthetic vein valve placement

Evaluation of prosthetic vein valves for deep venous valve insufficiency is still limited. In an animal study, De Borst percutaneously delivered a venous valve prosthesis (glutaraldehyde-fixed bovine vein sutured to a self-expanding Nitinol stent) via the porcine extrajugular vein into the iliac vein [102]. The animals were randomly given either vitamin K antagonists or a combination of aspirin and clopidogrel. Among 8 valves, 7 were patent (3 competent) in animals receiving vitamin K antagonists, whereas 5 out of 10 valves were patent (3 competent) in animals receiving aspirin and clopidogrel. After a phase I trial [103], the prosthesis was redesigned (valve with pericardial tissue, increasing the radial stiffness of the Nitinol stent, and incorporating a heparin coating). Phase II clinical trials of the new prosthesis are being planned in Europe and the United States.

Pavcnik et al. also developed a percutaneously deployed venous valve prosthesis. The first-generation valve was composed of Nitinol or stainless steel wires and a sheath made of small-intestinal submucosa. Using a sheep model, 25 valves were placed into the jugular veins and 88% exhibited good function. The remaining 12% had decreased function due to valve tilting [104]. The prosthetic venous valves were also placed in 3 patients without subsequent complications. The second-generation prosthetic valve was modified to prevent tilting, and this achieved a success rate of 92% [105,106]. The third-generation valve was further modified to prevent possible contact of the leaflet portion with the vein wall and to ensure continuous leaflet coaptation. The authors also conducted a feasibility study with a percutaneously deployed autologous venous valve in an ovine model, and noted that patency and competency were retained for 3 months [107].

6.6. Venous valve surgery

To date, numerous techniques for venous valve reconstruction have been reported, including both internal and external venous valve repair, valve transposition, and venous valve transplantation [108–118]. A detailed review of venous valve surgery appeared in the first issue of this Journal [119]. However, the efficacy of these techniques for ulcer healing has been reported to be significantly lower in patients with PTS than these with primary valvular insufficiency [120]. In contrast, Maleti and Lugli proposed a new neovalve construction technique involving flap creation [121]. In 17 limbs treated by neovalve construction, postoperative surveillance demonstrated a significant improvement in venous hemodynamics. Lugli et al. further modified their technique, and found a significant improvement in valvular competency [122]. In 2011, Maleti and Perrin described the results of various venous valve reconstruction techniques [123], and concluded that, in terms of clinical outcome, Maleti neovalve construction achieved better results than valvuloplasty, valve transposition or valve transplantation.

7. Conclusion

PTS is a common problem following DVT, and its clinical features range from minimum symptoms to disabling venous ulcers. In order to reduce the incidence of PTS, early clot lysis may be the key to restoring patency and potentially preserving valve function. Recent advances in endovascular catheter procedures provide better clot lysis than standard oral anticoagulant therapy. However, DOACs have been proven to show earlier lytic efficacy than vitamin K antagonists in experimental models. Extended anticoagulation with DOACs may be promising for reducing the risk of PTS in comparison with standard anticoagulant therapy. The application of ECSs after DVT has been widely accepted to prevent the development of PTS. Currently, however, the efficacy of ECSs for preventing PTS is controversial. For patients with established PTS, the treatment options are still limited. The use of a neuromuscular electrostimulator device may reduce the chronic symptoms of PTS. Stenting of the chronic obstructive iliac venous segment improves venous outflow and clinical symptoms. Development of bioprosthetic venous valves and related clinical trials are still ongoing. Although attempts at preventing PTS using open venous surgery have met with limited success, a new neovalve construction technique has demonstrated better clinical outcomes than previously reported venous valve surgery. These new developments may be beneficial for reducing the incidence of PTS in the future.

Conflict of interest

The author has no conflicts of interest to declare.

References

[1] P. Prandoni, A.W. Lensing, M.H. Prins, M. Frulla, A. Marchiori, E. Bernardi, D. Tormene, L. Mosena, A. Pagnan, A. Girolami, Below-knee elastic compression stockings to prevent the post-thrombotic syndrome: a randomized, controlled trial, Ann. Intern. Med. 141 (2004) 249–256.

[2] S.R. Kahn, I. Shrier, J.A. Julian, T. Ducruet, L. Arsenault, M.J. Miron, A. Roussin, S. Desmarais, F. Joyal, J. Kassis, S. Solymoss, L. Desjardins, D.L. Lamping, M. Johri, J.S. Ginsberg, Determinants and time course of the post-thrombotic syndrome after acute deep venous thrombosis, Ann. Intern. Med. 149 (2008) 698–707.

[3] S.R. Kahn, H. Partsch, S. Vedantham, P. Prandoni, C. Kearon, Definition of post-thrombotic syndrome of the leg for use in clinical investigations: a recommendation for standardization, J. Thromb. Haemost. 7 (2009) 879–883.

[4] S. Kachroo, D. Boyd, B.K. Bookhart, J. LaMori, J.R. Schein, D.J. Rosenberg, M. W. Reynolds, Quality of life and economic costs associated with post-thrombotic syndrome, Am. J. Health Syst. Pharm. 69 (2012) 567–572.

[5] S. Villalta, P. Bagatella, A. Piccioli, A.W. Lensing, M.H. Prins, P. Prandoni, Assessment of validity and reproducibility of a clinical scale for the post-thrombotic syndrome (abstract), Haemostasis 24 (1994) 158a.

[6] J.S. Ginsberg, F. Turkstra, H.R. Buller, B. MacKinnon, D. Magier, J. Hirsh, Postthrombotic syndrome after hip or knee arthroplasty: a crosssectional study, Arch. Intern. Med. 160 (2000) 669–672.

[7] D.P. Brandjes, H.R. Buller, H. Heijboer, M.V. Huisman, M. de Rijk, H. Jagt, et al., Randomised trial of effect of compression stockings in patients with symptomatic proximal-vein thrombosis, Lancet 349 (1997) 759–762.

[8] L. Widmer, H. Stathelin, C. Nissen, Sd. Venen-, Arterien-, Krankheiten, koronaire Herzkrankhei bei berufstatigen, Bern: Verlag Hans Huber, 1981.

[9] B. Eklöf, R.B. Rutherford, J.J. Bergan, P.H. Carpentier, P. Gloviczki, R.L. Kistner, M.H. Meissner, G.L. Moneta, K. Myers, F.T. Padberg, M. Perrin, C.V. Ruckley, P. C. Smith, T.W. Wakefield, American venous forum international ad hoc committee for revision of the CEAP classification. Revision of the CEAP classification for chronic venous disorders: consensus statement, J. Vasc. Surg. 40 (2004) 1248–1252.

[10] M.A. Vasquez, E. Rabe, R.B. McLafferty, C.K. Shortell, W.A. Marston, D. Gillespie, M.H. Meissner, R.B. Rutherford, American Venous Forum Ad Hoc Outcomes Working Group, Revision of the venous clinical severity score: venous outcomes consensus statement: special communication of the American Venous Forum ad hoc outcome working group, J. Vasc. Surg. 52 (2010) 1387–1396.

[11] D.N. Kolbach, M.W. Sandbrink, H.A. Neumann, M.H. Prins, Compression therapy for treating stage I and II (Widmer) post-thrombotic syndrome, Cochrane Database Syst. Rev. (2003) 4.

[12] A. Soosainathan, H.M. Moore, M.S. Gohel, A.H. Davies, Scoring systems for the post-thrombotic syndrome, J. Vasc. Surg. 57 (2013) 254–261.

[13] S.R. Kahn, S. Desmarais, T. Ducruet, L. Arsenault, J.S. Ginsberg, Comparison of the Villalta and Ginsberg clinical scales to diagnose the post-thrombotic syndrome: correlation with patient-reported disease burden and venous valvular reflux, J. Thromb. Haemost. 4 (2006) 907–908.

[14] T. Yamaki, A. Hamahata, K. Soejima, T. Kono, M. Nozaki, H. Sakurai, Factors predicting development of post-thrombotic syndrome in patients with a first episode of deep vein thrombosis: preliminary report, Eur. J. Vasc. Endovasc. Surg. 41 (2011) 126–133.

[15] E.M. Roumen-Klappe, M.C. Janssen, J. Van Rossum, S. Holewijn, M.M. Van Bokhoven, K. Kaasjager, et al., Inflammation in deep vein thrombosis and the development of post-thrombotic syndrome: a prospective study, J. Thromb. Haemost. 7 (2009) 582–587.

[16] E.M. Roumen-Klappe, M. den Heijer, M.C. Janssen, C. van der Vleuten, T. Thien, H. Wollersheim, The post-thrombotic syndrome: incidence and prognostic value of non-invasive venous examinations in a six-year follow-up study, Thromb. Haemost. 94 (2005) 825–830.

[17] C.R. Lattimer, Kalodiki, M. Azzam, G. Geroulakos, Validation of the Villalta scale in assessing post-thrombotic syndrome using clinical, duplex, and hemodynamic comparators, J. Vasc. Surg.: Venous Lymphat. Dis. 2 (2014) 8–14.

[18] A.I. Mekako, J. Hatfield, J. Bryce, D. Lee, P.T. McCollum, I. Chetter, A non-randomized controlled trial of endovenous laser therapy and surgery in the treatment of varicose veins, Ann. Vasc. Surg. 20 (2006) 451–457.

[19] L.H. Rasmussen, L. Bjoern, M. Lawaetz, A. Blemings, B. Lawaetz, B. Eklof, Randomized trial comparing endovenous laser ablation of the great saphenous vein with high ligation and stripping in patients with varicose veins: short-term results, J. Vasc. Surg. 46 (2007) 308–315.

[20] M.H. Meissner, C. Natiello, S.C. Nicholls, Performance characteristics of the venous clinical severity score, Vasc. Surg. 36 (2002) 889–895.

[21] J.J. Bergan, G.W. Schmid-Schonbein, P.D. Smith, A.N. Nicolaides, M. R. Boisseau, B. Eklof, Chronic venous disease, N. Engl. J. Med. 355 (2006) 488–498.

[22] K.B. Deatrick, J.L. Eliason, E.M. Lynch, A.J. Moore, N.A. Dewyer, M.R. Varma, C. G. Pearce, G.R. Upchurch, T.W. Wakefield, P.K. Henke, Vein wall remodeling after deep vein thrombosis involves matrix metalloproteinases and late fibrosis in a mouse model, J. Vasc. Surg. 42 (2005) 140–148.

[23] A. Laser, M. Elfline, C. Luke, D. Slack, A. Shah, V. Sood, B. Deatrick, B. McEvoy, C. Ostra, A. Comerota, S. Kunkel, C. Hogaboam, P.K. Henke, Deletion of cysteine-cysteine receptor 7 promotes fibrotic injury in experimental post-thrombotic vein wall remodeling, Arterioscler. Thromb. Vasc. Biol. 34 (2) (2014) 377–385.

[24] L.W. Tick, M.H. Kramer, F.R. Rosendaal, W.R. Faber, C.J. Doggen, Risk factors for post-thrombotic syndrome in patients with a first deep venous thrombosis, J. Thromb. Haemost. 6 (2008) 2075–2081.

[25] R.B. McLafferty, G.L. Moneta, M.A. Passman, et al., Late clinical and hemodynamic sequelae of isolated calf vein thrombosis, J. Vasc. Surg. 27 (1998) 50–56.

[26] S.R. Kahn, C. Kearon, J.A. Julian, B. Mackinnon, M.J. Kovacs, P. Wells, M. A. Crowther, D.R. Anderson, P. Van Nguyen, C. Demers, S. Solymoss, J. Kassis, W. Geerts, M. Rodger, J. Hambleton, J.S. Ginsberg, Extended Low-intensity Anticoagulation for Thrombo-embolism (ELATE) Investigators, Predictors of the post thrombotic syndrome during long-term treatment of proximal deep vein thrombosis, J. Thromb. Haemost. 3 (2005) 718–723.

[27] P. Prandoni, A. Lensing, A. Cogo, et al., The long-term clinical course of acute deep venous thrombosis, Ann. Intern. Med. 125 (1996) 1–7.

[28] P. Prandoni, A.W.A. Lensing, M.H. Prins, et al., Below-knee elastic compression stockings to prevent the postthrombotic syndrome: a randomized, controlled trial, Ann. Intern. Med. 141 (2004) 249–256.

[29] C.J. Van Dongen, P. Prandoni, M. Frulla, et al., Relation between quality of anticoagulant treatment and the development of the postthrombotic syndrome, J. Thromb. Haemost. 3 (2005) 939–942.

[30] N. Labropoulos, A.P. Gasparis, A.K. Tassiopoulos, Prospective evaluation of the clinical deterioration in post-thrombotic limbs, J. Vasc. Surg. 50 (2009) 826–830.

[31] R.D. Hull, G.E. Raskob, D. Rosenbloom, A.A. Panju, P. Brill-Edwards, J. S. Ginsberg, et al., Heparin for 5 days as compared with 10 days in the initial treatment of proximal venous thrombosis, N. Engl. J. Med. 322 (1990) 1260–1264.

[32] R.D. Hull, G.F. Pineo, R. Brant, J. Liang, R. Cook, S. Solymoss, et al., Home therapy of venous thrombosis with long-term LMWH versus usual care: patient satisfaction and post-thrombotic syndrome, Am. J. Med. 122 (762–9) (2009) e763.

[33] L. Young, P. Ockelford, D. Milne, et al., Posttreatment residual thrombus increases the risk of recurrent deep vein thrombosis and mortality, J. Thromb. Haemost. 4 (2006) 1919–1924.

[34] C.T. Ammollo, F. Semeraro, F. Incampo, N. Semeraro, M. Colucci, Dabigatran enhances clot susceptibility to fibrinolysis by mechanisms dependent on and independent of thrombin-activatable fibrinolysis inhibitor, J. Thromb. Haemost. 8 (2010) 790–798.

[35] M. Blombäck, S. He, N. Bark, H.N. Wallen, M. Elg, Effects on fibrin network porosity of anticoagulants with different modes of action and reversal by activated coagulation factor concentrate, Br. J. Haematol. 152 (2011) 758–765.

[36] S.A. Shaya, L.J. Saldanha, N. Vaezzadeh, J. Zhou, R. Ni, P.L. Gross, Comparison of the effect of dabigatran and dalteparin on thrombus stability in a murine model of venous thromboembolism, J. Thromb. Haemost. 6 (14) (2015) 143–152.

[37] S. Schulman, A.S. Rhedin, P. Lindmarker, A. Carlsson, G. Lärfars, P. Nicol, E. Loogna, E. Svensson, B. Ljungberg, H. Walter, A comparison of six weeks with six months of oral anticoagulant therapy after a first episode of venous thromboembolism, N. Engl. J. Med. 332 (1995) 1661–1665.

[38] T. Baglin, R. Luddington, K. Brown, C. Baglin, Incidence of recurrent venous thromboembolism in relation to clinical and thrombophilic risk factors: prospective cohort study, Lancet 362 (2003) 523–526.

[39] S.R. Kahn, C. Kearon, J.A. Julian, et al., Predictors of the postthrombotic syndrome during long-term treatment of proximal deep vein thrombosis, J. Thromb. Haemost. 3 (2005) 718–723.

[40] R.S. Chitsike, M.A. Rodger, M.J. Kovacs, M.T. Betancourt, P.S. Wells, D. R. Anderson, I. Chagnon, G. Le Gal, S. Solymoss, M.A Crowther, A. Perrier, R. H. White, L.M. Vickars, T. Ramsay, S.R. Kahn, Risk of post-thrombotic syndrome after subtherapeutic warfarin anticoagulation for a first unprovoked deep vein thrombosis: results from the REVERSE study, J. Thromb. Haemost. 10 (2012) 2039–2044.

[41] N. Labropoulos, T. Waggoner, W. Sammis, S. Samali, P.J. Pappas, The effect of venous thrombus location and extent on the development of post-thrombotic signs and symptoms, J. Vasc. Surg. 48 (2008) 407–412.

[42] A.J. Comerota, N. Grewal, J.T. Martinez, J.T. Chen, R. Disalle, L. Andrews, D. Sepanski, Z. Assi, Postthrombotic morbidity correlates with residual thrombus following catheter-directed thrombolysis for iliofemoral deep vein thrombosis, J. Vasc. Surg. 55 (2012) 768–773.

[43] T. Yamaki, M. Nozaki, H. Sakurai, M. Takeuchi, K. Soejima, T. Kono, High peak reflux velocity in the proximal deep veins is a strong predictor of advanced post-thrombotic sequelae, J. Thromb. Haemost. 5 (2007) 305–312.

[44] J. Latella, S. Desmarais, M.J. Miron, A. Roussin, F. Joyal, J. Kassis, S. Solymoss, L. Desjardins, J.S. Ginsberg, S.R. Kahn, Relation between D-dimer level, venous valvular reflux and the development of post-thrombotic syndrome after deep vein thrombosis, J. Thromb. Haemost. 8 (2010) 2169–2175.

[45] J.P. Galanaud, C.A. Holcroft, M.A. Rodger, M.J. Kovacs, M.T. Betancourt, P. S. Wells, D.R. Anderson, I. Chagnon, G. Le Gal, S. Solymoss, M.A. Crowther, A. Perrier, R.H. White, L.M. Vickars, T. Ramsay, S.R. Kahn, Predictors of post-thrombotic syndrome in a population with a first deep vein thrombosis and no primary venous insufficiency, J. Thromb. Haemost. 11 (2013) 474–480.

[46] F. Gabriel, M. Labiós, O. Portolés, M. Guillén, D. Corella, F. Francés, M. Martínez, J. Gil, C. Saiz, Incidence of post-thrombotic syndrome and its association with various risk factors in a cohort of Spanish patients after one year of follow-up following acute deep venous thrombosis, Thromb. Haemost. 92 (2004) 328–336.

[47] P.J. Marchena Yglesias, J.A. Nieto Rodriguez, S. Serrano Martinez, O. Belinchón

Moya, A. Cortés Carmona, A. Díaz de Tuesta, M.J. Bruscas Alijarde, M.D. Ruiz Ribó, Acute-phase reactants and markers of inflammation in venous thromboembolic disease: correlation with clinical and evolution parameters, An. Med. Interna 23 (2006) 105–110.
[48] A. Rabinovich, J.M. Cohen, S.R. Kahn, Predictive value of markers of inflammation in the postthrombotic syndrome: a systematic review Inflammatory biomarkers and PTS, Thromb. Res. 136 (2015) 289–297.
[49] R.N. Harada, M.L. Katz, A.J. Comerota, A noninvasive screening test to detect critical deep venous reflux, J. Vasc. Surg. 22 (1995) 532–537.
[50] D.C. Christopoulos, G. Belcaro, A.N. Nicolaides, The hemodynamic effect of venous hypertension in the microcirculation of the lower limb, J. Cardiovasc. Surg. (Torino) 36 (1995) 403–406.
[51] M. Skladany, H. Schanzer, Increased arterial inflow in extremities with chronic venous insufficiency: an important and unappreciated hemodynamic parameter, Surgery 120 (1996) 30–33.
[52] S. Raju, R. Fredericks, Venous obstruction: an analysis of one hundred thirty-seven cases with hemodynamic, venographic, and clinical correlations, J. Vasc. Surg. 14 (1991) 305–313.
[53] D.J. Paolini, A.J. Comerota, L.S. Jones, Lower extremity arterial inflow is adversely affected in patients with venous disease, J. Vasc. Surg. 48 (2008) 960–964.
[54] Y. Hosoi, H. Yasuhara, H. Shigematsu, H. Aramoto, T. Komiyama, T. Muto, A new method for the assessment of venous insufficiency in primary varicose veins using near-infrared spectroscopy, J. Vasc. Surg. 26 (1997) 53–60.
[55] Y. Hosoi, H. Yasuhara, H. Shigematsu, T. Komiyama, A. Onozuka, T. Muto, Influence of popliteal venous thrombosis on subsequent ambulatory venous function measured by near-infrared spectroscopy, Am. J. Surg. 177 (1999) 111–116.
[56] T. Yamaki, M. Nozaki, H. Sakurai, Y. Kikuchi, K. Soejima, T. Kono, A. Hamahata, K. Kim, Prognostic impact of calf muscle near-infrared spectroscopy in patients with a first episode of deep vein thrombosis, J. Thromb. Haemost. 7 (2009) 1506–1513.
[57] T. Yamaki, A. Hamahata, K. Soejima, T. Kono, M. Nozaki, H. Sakurai, Factors predicting development of post-thrombotic syndrome in patients with a first episode of deep vein thrombosis: preliminary report, Eur. J. Vasc. Endovasc. Surg. 41 (2011) 126–133.
[58] T. Yamaki, H. Konoeda, A. Osada, A. Hamahata, T. Kono, K. Soejima, M. Nozaki, H. Sakurai, Measurements of calf muscle oxygenation during standing and exercise in patients with primary valvular insufficiency, J. Vasc. Surg.: Venous Lymphat. Dis. 1 (2013) 333–340.
[59] T. Yamaki, H. Konoeda, A. Osada, A. Hamahata, T. Kono, K. Soejima, M. Nozaki, H. Sakurai, Measurements of calf muscle oxygenation during light-intensity exercise in patients with post-thrombotic, J. Vasc. Surg.: Venous Lymphat. Dis. 2 (2014) 424–432.
[60] T. Yamaki, Y. Hasegawa, A. Osada, H. Konoeda, A. Hamahata, O. Masakazu, M. Nozaki, H. Sakurai, Time taken to the maximum increase in the oxygenated hemoglobin level in calf muscle as a predictor of mild to moderate postthrombotic syndrome, J. Vasc. Surg.: Venous Lymphat. Dis. (2016), In press.
[61] C. Kearon, E.A. Akl, J. Ornelas, A. Blaivas, D. Jimenez, H. Bounameaux, M. Huisman, C.S. King, T.A. Morris, N. Sood, S.M. Stevens, J.R. Vintch, P. Wells, S.C. Woller, L. Moores, Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report, Chest 149 (2016) 315–352.
[62] S. Schulman, P. Lindmarker, M. Holmstrom, G. Larfars, A. Carlsson, P. Nicol, E. Svensson, B. Ljungberg, S. Viering, S. Nordlander, B. Leijd, K. Jahed, M. Hjorth, O. Linder, M. Beckman, Postthrombotic syndrome, recurrence, and death 10 years after the first episode of venous thromboembolism treated with warfarin for 6 weeks or 6 months, J. Thromb. Haemost. 4 (2006), 743–42.
[63] J.A. González-Fajardo, M. Martin-Pedrosa, J. Castrodeza, S. Tamames, C. Vaquero-Puerta, Effect of the anticoagulant therapy in the incidence of post-thrombotic syndrome and recurrent thromboembolism: comparative study of enoxaparin versus coumarin, J. Vasc. Surg. 48 (2008) 953–959.
[64] H. Partsch, Compression therapy of the legs. A review, J. Dermatol. Surg. Oncol. 17 (1991) 799–805.
[65] A.D. Giannoukas, N. Labropoulos, J.A. Michaels, Compression with or without early ambulation in the prevention of postthrombotic syndrome: a systematic review, Eur. J. Vasc. Endovasc. Surg. 32 (2006) 217–221.
[66] S.K. Kakkos, S.S. Daskalopoulou, M.E. Daskalopoulos, A.N. Nicolaides, G. Geroulakos, Review on the value of graduated elastic compression stockings after deep vein thrombosis, Thromb. Haemost. 96 (2006) 441–445.
[67] D. Kolbach, M. Sandbrink, H. Neumann, M. Prins, Compression therapy for treating stage I and II (Widmer) postthrombotic syndrome, Cochrane Database Syst. Rev. (2003), CD004177.
[68] S.R. Kahn, S. Shapiro, P.S. Wells, M.A. Rodger, M.J. Kovacs, D.R. Anderson, V. Tagalakis, A.H. Houweling, T. Ducruet, C. Holcroft, M. Johri, S. Solymoss, M. J. Miron, E. Yeo, R. Smith, S. Schulman, J. Kassis, C. Kearon, I. Chagnon, T. Wong, C. Demers, R. Hanmiah, S. Kaatz, R. Selby, S. Rathbun, S. Desmarais, L. Opatrny, T.L. Ortel, J.S. Ginsberg, SOX trial investigators. Compression stockings to prevent post-thrombotic syndrome: a randomised placebo-controlled trial, Lancet 383 (2014) 880–888.
[69] C.F. Berntsen, A. Kristiansen, E.A. Akl, P.M. Sandset, E.M. Jacobsen, G. Guyatt, P.O. Vandvik, Compression stockings for preventing the postthrombotic syndrome in patients with deep vein thrombosis, Am. J. Med. 129 (2016) 447. e1–447.e20.
[70] H. Akesson, L. Brudin, J.A. Dahlstrom, B. Eklof, P. Ohlin, G. Plate, Venous function assessed during a 5 year period after acute ilio-femoral venous thrombosis treated with anticoagulation, Eur. J. Vasc. Surg. 4 (1990) 43–48.
[71] K.T. Delis, D. Bountouroglou, A.O. Mansfield, Venous claudication in iliofemoral thrombosis: long-term effects on venous hemodynamics, clinical status, and quality of life, Ann. Surg. 239 (2004) 118–126.
[72] L. Watson, M.P. Armon, Thrombolysis for acute deep vein thrombosis (review), Cochrane Database Syst. Rev. (2004) 4.
[73] M.S. Elliot, E.J. Immelman, P. Jeffery, S.R. Benatar, M.R. Funston, J.A. Smith, B. J. Shepstone, A.D. Ferguson, P. Jacobs, W. Walker, J.H. Louw, A comparative randomised trial of heparin versus streptokinase in the treatment of acute proximal venous thrombosis: an interim report of a prospective trial, Br. J. Surg. 66 (1979) 838–843.
[74] H. Arnesen, A. Heilo, E. Jakobsen, B. Ly, E. Skaga, A prospective study of streptokinase and heparin in the treatment of deep venous thrombosis, Acta Med. Scand. 203 (1978) 457–463.
[75] S.Z. Goldhaber, M.F. Meyerovitz, D. Green, R.L. Vogelzang, P. Citrin, J. Heit, M. Sobel, H.B. Wheeler, D. Plante, H. Kim, Randomised controlled trial of tissue plasminogen activator in proximal deep venous thrombosis, Am. J. Med. 88 (1990) 235–240.
[76] A.J. Comerota, R.C. Throm, S.D. Mathias, S. Haughton, M. Mewissen, Catheter-directed thrombolysis for iliofemoral deep venous thrombosis improves health-related quality of life, J. Vasc. Surg. 32 (2000) 130–137.
[77] M. Elsharawy, E. Elzayat, Early results of thrombolysis vs anticoagulation in iliofemoral venous thrombosis. A randomized clinical trial, Eur. J. Vasc. Endovasc. Surg. 24 (2002) 209–214.
[78] T. Enden, N.E. Kløw, L. Sandvik, C.E. Slagsvold, W. Ghanima, G. Hafsahl, P. A. Holme, L.O. Holmen, A.M. Njaastad, G. Sandbaek, P.M. Sandset, Catheter-directed thrombolysis vs. anticoagulant therapy alone in deep vein thrombosis: results of an open randomized, controlled trial reporting on short-term patency, J. Thromb. Haemost. 7 (2009) 1268–1275.
[79] Y. Haig, T. Enden, O. Grøtta, N.E. Kløw, C.E. Slagsvold, W. Ghanima, L. Sandvik, G. Hafsahl, P.A. Holme, L.O. Holmen, A.M. Njaaastad, G. Sandbæk, P. M. Sandset, (CaVenT Study Group), Post-thrombotic syndrome after catheter-directed thrombolysis for deep vein thrombosis (CaVenT): 5-year follow-up results of an open-label, randomised controlled trial, Lancet Haematol. 3 (2016) e64–e71.
[80] S. Vedantham, S.Z. Goldhaber, S.R. Kahn, J. Julian, E. Magnuson, M.R. Jaff, T. P. Murphy, D.J. Cohen, A.J. Comerota, H.L. Gornik, M.K. Razavi, L. Lewis, C. Kearon, Rationale and design of the ATTRACT study – a multicenter randomized trial to evaluate pharmacomechanical catheter-directed thrombolysis for the prevention of post-thrombotic syndrome in patients with proximal deep vein thrombosis, Am. Heart J. 165 (523–530) (2013) e3.
[81] R.P. Engelberger, J. Fahrni, T. Willenberg, F. Baumann, D. Spirk, N. Diehm, D. D. Do, I. Baumgartner, N. Kucher, Fixed low-dose ultrasound-assisted catheter-directed thrombolysis followed by routine stenting of residual stenosis for acute ilio-femoral deep-vein thrombosis, Thromb. Haemost. 111 (2014) 1153–1160.
[82] A. Karthikesalingam, E.L. Yound, R.J. Hinchliffe, I.M. Loftus, M.M. Thmpson, P. J.E. Holt, A systematic review of percutaneous mechanical thrombectomy in the treatment of deep venous thrombosis, Eur. J. Vasc. Endovasc. Surg. 41 (2011) 554–565.
[83] G. Plate, B. Eklöf, L. Norgren, P. Ohlin, J.A. Dahlström, Venous thrombectomy for iliofemoral vein thrombosis – 10 year results of a prospective randomised study, Eur. J. Vasc. Endovasc. Surg. 14 (1997) 367–374.
[84] J.S. Ginsberg, J. Hirsh, J. Julian, M. van der Laandevries, D. Magier, B. MacKinnon, M. Gent, Prevention and treatment of postphlebitic syndrome: results of a 3-part study, Arch. Intern. Med. 161 (2001) 2105–2109.
[85] A.I. Volikova, J. Edwards, M.C. Stacey, H.J. Wallace, High-frequency ultrasound measurement for assessing post-thrombotic syndrome and monitoring compression therapy in chronic venous disease, J. Vasc. Surg. 50 (2009) 820–825.
[86] P.C. Smith, S. Sarin, J. Hasty, J.H. Scurr, Sequential gradient pneumatic compression enhances venous ulcer healing: a randomized trial, Surgery 108 (1990) 871–875.
[87] J.S. Ginsberg, D. Magier, B. Mackinnon, M. Gent, J. Hirsh, Intermittent compression units for severe post-phlebitic syndrome: a randomized crossover study, CMAJ 160 (1999) 1303–1306.
[88] A.J. Comerota, V. Chouhan, R.N. Harada, L. SUn, J. Hosking, R. Veemansunemi, A.J. Comerota Jr, D. Schlappy, A.K. Rao, The fibrinolytic effect of intermittent compression: mechanism of enhanced fibrinolysis, Ann. Surg. 226 (1997) 306–313.
[89] M.J. O'Donell, S. McRae, S.R. Kahn, J.A. Julian, C. Kearon, B. Mackinnon, D. Maqier, C. Strulovich, T. Lyons, S. Robinson, J. Hirsh, J.S. Ginsberg, Evaluation of a venous-return assist device to treat severe post-thrombotic syndrome (VENOPTS). A randomized control trials, Thromb. Haemost. 99 (2008) 623–629.
[90] H. Jawad, D.S. Bain, H. Dawson, K. Crawford, A. Johnston, A. Tucker, The effectiveness of a novel neuromuscular electrostimulation method versus intermittent pneumatic compression in enhancing lower limb blood flow, J. Vasc. Surg.: Venous Lymphat. Dis. 2 (2014) 160–165.
[91] M.B. Griffin, D. Bond, A. Nicolaides, Measurement of blood flow in the deep veins of the lower limbs using the geko™ neuromuscular electrostimulation device, Int. Angiol. (2016), Epub ahead of print.
[92] J.A. Summer, J. Clinch, M. Radhakrishnan, A. Healy, V. McMillan, E. Morris, T. Rua, M. Ofuya, Y. Wang, P.W. Dimmock, C. Lewis, J.L. Peacock, S.E. Keevil, The geko™ electro-stimulation device for venous thromboembolism

prophylaxis: a NICE medical technology guidance, Appl. Health Econ. Health Policy 13 (2015) 135–147.
[93] A.B. Jull, B. Arroll, V. Parag, J. Waters, Pentoxifylline for treating venous leg ulcers, Cochrane Database Syst. Rev. (2007) 3.
[94] J.R. Morling, S.E. Yeoh, D.N. Kolbach, Rutosides for treatment of post-thrombotic syndrome, Cochrane Database Syst. Rev. (2015) 16.
[95] M.H. Pittler, E. Ernst, Horse chestnut seed extract for chronic venous insufficiency, Cochrane Database Syst. Rev. (2012) 11.
[96] S.R. Kahn, I. Shrier, S. Shapiro, A.H. Houweling, A.M. Hirsch, R.D. Reid, C. Kearon, K. Rabhi, M.A. Rodger, M.J. Kovacs, D.R. Anderson, P.S. Wells, Six-month exercise training program to treat post-thrombotic syndrome: a randomized controlled two-centre trial, CMAJ 183 (2011) 37–44.
[97] T. Kölbel, M. Lindh, M. Akesson, J. Wassèlius, A. Gottsäter, K. Ivancev, Chronic iliac vein occlusion: midterm results of endovascular recanalization, J. Endovasc. Ther. 16 (2009) 483–491.
[98] P. Neglen, M.A. Berry, S. Raju, Endovascular surgery in the treatment of chronic primary and post-thrombotic iliac vein obstruction, Eur. J. Vasc. Endovasc. Surg. 20 (2000) 560–571.
[99] K.T. Delis, H. Bjarnason, P.W. Wennburg, T.W. Rooke, P. Gloviczki, Successful iliac vein and inferior vena cava stenting ameliorates venous claudication and improves venous outflow, calf muscle pump function, and clinical status in post-thrombotic syndrome, Ann. Surg. 245 (2007) 130–139.
[100] S. Raju, Best management options for chronic iliac vein stenosis and occlusion, J. Vasc. Surg. 57 (2013) 1163–1169.
[101] W. Wen-da, Z. Yu, C. Yue-Xin, Stenting for chronic obstructive venous disease: a current comprehensive meta-analysis and systematic review, Phlebology (2015), Epub ahead of print.
[102] G.J. de Borst, J.A. Teijink, M. Patterson, T.C. Quijano, F.L. Moll, A percutaneous approach to deep venous valve insufficiency with a new self-expanding venous frame valve, J. Endovasc. Ther. 10 (2003) 341–349.
[103] S.S. Gale, S. Shuman, H.G. Beebe, J.P. Pigott, A.J. Comerota, Percutaneous venous valve bioprosthesis: initial observations, Vasc. Endovasc. Surg. 38 (2004) 221–224.
[104] D. Pavcnik, L. Machan, B. Uchida, J. Kaufman, F.S. Keller, J. Rösch, Percutaneous prosthetic venous valves: current state and possible applications, Tech. Vasc. Interv. Radiol. 6 (2003) 137–142.
[105] D. Pavcnik, J. Kaufman, B. Uchida, L. Correa, T. Hiraki, S.C. Kyu, F.S. Keller, J. Rosch, Second-generation percutaneous bioprosthetic valve: a short-term study in sheep, J. Vasc. Surg. 40 (2004) 1223–1227.
[106] D. Pavcnik, J.A. Kaufman, B.T. Uchida, B. Case, L.O. Correa, A.Y. Goktay, A. Hamada, F.S. Keller, J. Rösch, Significance of spatial orientation of percutaneously placed bioprosthetic venous valves in an ovine model, J. Vasc. Interv. Radiol. 16 (2005) 1511–1516.
[107] D. Pavcnik, Q. Yin, B. Uchida, W.K. Park, H. Hoppe, M.D. Kim, F.S. Keller, J. Rösch, Percutaneous autologous venous valve transplantation: short-term feasibility study in an ovine model, J. Vasc. Surg. 46 (2007) 338–345.
[108] R.L. Kistnet, Surgical repair of a venous valve, Straub Clin. Proc. 34 (1968) 41–43.
[109] S.A. Taheri, L. Lazar, S. Elias, P. Marchand, R. Heiffiner, Surgical treatment of postphlebitic syndrome with vein valve transplant, Am. J. Surg. 144 (1982) 221–224.
[110] S. Raju, Venous insufficiency of the lower limbs and stasis ulceration, Ann. Surg. 197 (1983) 688–697.
[111] V.S. Sottiurai, Technique in direct venous valvuloplasty, J. Vasc. Surg. 8 (1988) 646–648.
[112] R.L. Kistner, Surgical technique of the external venous valve repair, Straub Found Proc. (1990), 15ff.
[113] P. Gloviczki, S.W. Merrell, T.C. Bower, Femoral vein valve repair under direct vision without venotomy: a modified technique with use of angioscopy, J. Vasc. Surg. 14 (1991) 645–648.
[114] J.D. Bry, P.A. Muto, T.F. O'Donell, L.A. Isaacson, The clinical and hemodynamic results after axillary-to-popliteal vein valve transplantation, J. Vasc. Surg. 21 (1995) 110–119.
[115] S. Raju, P. Neglen, J. Doolittle, E.F. Meydrech, Axillary vein transfer in trabeculated post-thrombotic veins, J. Vasc. Surg. 29 (1999) 1050–1062.
[116] S. Raju, M.A. Berry, P. Neglen, Transcommissural valvuloplasty: technique and results, J. Vasc. Surg. 32 (2000) 969–976.
[117] S.M. Wang, Z.J. Hu, S.Q. Li, X.L. Hang, C.S. Ye, Effect of external valvuloplasty of deep vein in the treatment of chronic venous insufficiency of the lower extremity, J. Vasc. Surg. 44 (2006) 1296–1300.
[118] L. Kabbani, G.A. Escobar, F. Mansour, T.W. Wakefield, P.K. Henke, Longevity and outcomes of axillary valve transplantation for severe lower extremity chronic venous insufficiency, Ann. Vasc. Surg. 25 (2011) 496–501.
[119] A. Caggiati, L. Caggiati, Surgery of venous valve, Rev. Vasc. Med. 1 (2013) 15–23.
[120] E.M. Masuda, R. Kistner, Long-term results of venous valve reconstruction: a four- to twenty-one year follow up, J. Vasc. Surg. 19 (1994) 391–403.
[121] O. Maleti, M. Lugli, Neovalve construction in postthrombotic syndrome, J. Vasc. Surg. 43 (2006) 794–799.
[122] M. Lugli, S. Guerzoni, M. Garofalo, G. Smedile, O. Maleti, Neovalve construction in deep venous incompetence, J. Vasc. Surg. 49 (2009) 156–162.
[123] O. Maleti, M. Perrin, Reconstructive surgery for deep vein reflux in the lower limbs: techniques, results and indications, Eur. J. Vasc. Endovasc. Surg. 41 (2011) 837–848.